REMARKS

Claims 8-12, 19-31, 34-51 and 55-74 are pending in the application. Claims 29-31, 37-45 and 59-66 are withdrawn from consideration as being drawn to non-elected inventions. Claims 73 and 74 are allowed. Claims 8, 19, 21, 24, 27, 34, 35, 36, 46, 47, 50, 51, 55 and 57 have been amended to better clarify what Applicants regard as the invention. Claims 12, 22, 23, 25, 26, 28 and 48 have been canceled without prejudice or disclaimer. Support for the amendments can be found throughout the specification, in particular on page 6, lines 7-24; on page 7, lines 1-15; on page 10, lines 3-30; on page 11, lines 15-19 and 22-26; on page 28, lines 3-30 through page 29, lines 1-29; on page 30, lines 1-29; on page 31, lines 1-18; on page 36, lines 18-23; on page 38, lines 20-30 through page 39, lines 1-30 and on to page 40, lines 1-8. Support can also be found in the Examples 1-4 on pages 41-52 and in the claims as originally filed. No new matter has been added by way of this amendment. Thus, as a result of the foregoing amendment, claims 8-11, 19-21, 24, 27, 34-36, 46-47, 49-51, 55-58 and 67-74 remain pending. Reconsideration of this application is respectfully requested.

Rejections under 35 U.S.C. §112

Claims 8-12, 19-28,34-36,46-51,55-58 and 67-72 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. More particularly, the Examiner alleges that while the specification is enabled for "increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF or NF-PO4 in the bone marrow or neural cells", "promoting growth or differentiation of neural precursor cells" or "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetarnide-treated animal to a site of injury in animal", does not reasonably provide enablement for "promoting neural cell growth or differentiation", "promoting recovery of cells expressing neuronal progenitor cell markers after injury to the neuronal cells", "promoting neural cell growth or differentiation of neural cells" and "treating injury to neuronal cells", with the administration of compounds of formula (II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Examiner notes that the invention relates to promoting neural tissue regeneration or neural expression. Moreover, the specification defines neural tissue as "all tissue endogenous to the nervous system" (page 13, lines 10-12 and lines 22-26); neural expression as the expression of any proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells (page 13, lines 13-1 8); and neural progenitor cells as "any cell that can differentiate into a neural tissue cell, or be induced to differentiate into a neural tissue cell, including neural precursor cells, whether directly or through intermediate cell stages" (page 14, lines 1-3). As the specific embodiments of the invention, the instant specification discloses in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyI]phenyl]-acetamide in increasing neural expression of eNCAM, MAP 11, beta-tubulin, nestin, NF and NF-PO4 (Examples 1 and 2) and in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in increasing the growth of neurons or astrocytes (Example 4). The instant specification also discloses that animals (Fischer F344 female rats) treated with bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated donor animal demonstrates a decrease in cavity size at the contusion injury site, in vivo study (Example 3).

However, the Examiner alleges that the specification does not provide sufficient guidance for the skilled artisan to ascertain (i) which proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells other than the disclosed proteins, *eg.* eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4, and (ii) which neural tissues, neural precursor cells or progenitor cells other than bone marrow cells would be enabled in this invention in animals or human. Furthermore, the Examiner alleges that the specification does not provide sufficient guidance for the skilled artisan how to ascertain that (iii) the growth of neurons or astrocytes by the administration of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide *in vitro* would lead to the improvement of the functional recovery of neurons, and (iv) provide the effective treatment of complex neurodegenerative diseases or conditions that may have unrelated manifestation *in vivo*, without undue amount of experimentation.

The Examiner further alleges that the instant invention relates to methods of promoting neural cell growth or differentiation (claims 8-12, 34-36, 67-68); a method for promoting recovery of cells expressing neuronal progenitor cell markers after injury to the neuronal cells (claims 19-28); a method for treating injury to neuronal cells (claims 46-51,

55-56); a method for promoting growth and differentiation of neural precursor cells (claims 57-58), wherein methods requires the administration of compounds of formula II. More specifically, claims 34-36 and 57-58 are directed to a transplantation method.

The Examiner alleges that with the exception of "method of increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4", "promoting growth or differentiation of neural precursor cells" with the transplantation method described in claim 57 or "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated animal to a site of injury in animal", the skilled artisan cannot envision that (a) the administration of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide is capable of increasing the expression of other known neural proteins (e.g., vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN. FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...), and (b) promoting regeneration of diverse neural tissues, neural precursor cells, progenitor cells or tissue of neural origin (e.g., schwann cells, stem cells, oligodendrocytes, etc...) in animals or human; and (c) the administration of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide, without neutralizing the nerve-growth inhibitory properties of various proteins in the CNS environment, is capable of providing the desired effects of the claimed invention, particularly claims 8-12, 19-28, 46-56 and 67-72 where no transplantation method is required, in animals or human.

Moreover, the Examiner alleges that the breadth of the instant claims encompasses promotion of neural cells (e.g., stem cells, progenitor cells, neurons, glial cells, astrocytes, oligodendrites, etc...) the expression of neural proteins (e.g. eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4, vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN, FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...) or the treatment of complex neurodegenerative conditions (e.g., multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, sinile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing

panencephalitis, Hallerrorden-Spatz disease, Dementia pugilistica, etc...), that are known today, and those that may be discovered in the future.

For the reasons given above, in view of the nature of the invention, the amount of guidance present in the specification, the breadth of the claims, the relative skill of those in the art, and the predictability or unpredictability of the art, the Examiner alleges that it would take undue trials and errors to practice the invention as claimed.

Applicants respectfully traverse the Examiner's rejection and have amended the claims to better clarify aspects of the invention.

More particularly, Applicants have amended claim 8 to recite:

"A method for increasing neural expression of one or more proteins on neural precursor cells in vitro, wherein said one or more proteins are selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, comprising exposing said cells in vitro to an effective amount of a composition containing a compound having one of the following structural formulas..."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Examples 1 and 2, found on pages 41-45, and in Example 4 on pages 50-52. The results of these experiments, as depicted in photographs of the cell cultures, were provided to the Examiner with a Declaration under 37 C.F.R. §1.132 signed by Dr. Timothy Neuberger, and forwarded with the response to the Office Action dated November 5, 2004.

Furthermore, claim 19 has been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells in vitro, wherein said neural precursor cells express one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, the method comprising exposing said cells in vitro to an effective amount of a composition containing a compound having one of the following structural formulas..."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Examples 1 and 2 on pages 41-45 and in Example 4 on pages 50-52. As noted above, the results of these experiments, as depicted in

photographs of the cell cultures, were provided to the Examiner with a Declaration under 37 C.F.R. §1.132 signed by Dr. Timothy Neuberger, and forwarded with the response to the Office Action dated November 5, 2004.

More particularly, while Applicants respectfully traverse the Examiner's rejection, Applicants point out to the Examiner that the genesis and growth of neurons from neural precursor/progenitor cells is often preceded by the upregulation of a number of proteins, more particularly, those proteins as currently claimed. Support for this can be found in the instant application on page 6, lines 16-24, whereby it states:

> "The genesis or growth of neurons, for example from progenitor cells, is often preceded by the upregulation of a variety of proteins. For example, embryonic NCAM (eNCAM) is widely but transiently expressed early in embryogenesis. Likewise, subsequent expression of beta-tubulin and MAP-II are also indicative of the expression of proteins involved in the genesis and growth of nerve cells. The appearance of phosphorylated neurofilament protein subsequent to beta-tubulin and MAP-II are also markers of the genesis and growth of neurons. The methods of the invention promote the differentiation or growth of neural progenitor cells by the administration of certain compositions which are described below."

In addition, claim 34 has been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells in a mammal in need of such therapy, said cells expressing one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, comprising:

a) administering to a first mammal a neural precursor cell growth or differentiation promoting effective amount of a composition;

b) collecting a population of neural stem cells or neural progenitor cells from the first mammal; and

c) delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal; wherein the composition comprises a compound having one of the following structural formulas..."

Support for the claim amendment and for enablement of this aspect of the invention, as now claimed, can be found in Example 3 on pages 45-50.

Furthermore, claim 46 has been amended to recite:

"A method for treating an injury to nervous system tissue in a mammal, comprising collecting a population of neural stem cells or neural precursor cells obtained from a first mammal treated with a compound having one of the following structural formulas...

and administering said neural stem cells or neural precursor cells to a site having a nervous system injury in the first mammal or to a site having a nervous system injury in a second mammal."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Example 3 on pages 45-50 of the instant application.

In addition, claim 55 has been amended to recite:

"A method for increasing the number of neural precursor cells expressing one or more proteins selected from the group consisting of β-tubulin, MAP II, eNCAM and nestin, either in vitro, or in vivo at the site of injury, comprising one of the following:

I. a) obtaining a population of neural precursor cells; and

b) treating said cells in vitro with an effective amount of a composition containing a compound having one of the following structures.....; or

II. *a) administering an effective amount of a composition containing a compound having one of the following structures to a first mammal.....*

b) collecting a population of neural precursor cells from said first mammal; and

c) delivering said neural precursor cells to the site of injury in the first mammal or to a site of injury in a second mammal; wherein said delivery results in an increase in the number of neural precursor cells at the site of injury in the first or second mammal."

Support for this claim amendment and for enablement of this aspect of the invention can be found particularly in Example 3 on pages 45-50, and also on page 29, lines 2-29; on page 30, lines 1-29 continuing on to page 31, lines 1-18, and in the photographs provided to the Examiner with a Declaration under 37 C.F.R. §1.132 signed by Dr. Timothy Neuberger, and forwarded with the response to the Office Action dated November 5, 2004.

Furthermore, claim 57 has been amended to recite:

"A method for promoting growth and differentiation of neural precursor cells in a mammal in need of such therapy, comprising

(a) administering a population of neural precursor cells obtained from a first mammal treated with a compound having one of the following structural formulas.....

b) collecting neural precursor cells expressing one or more proteins selected from the group consisting of eNCAM and nestin, from said first mammal and delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal in need of such therapy."

Support for this claim amendment and for enablement of this aspect of the invention, as now claimed, can be found particularly in Example 3 on pages 45-50 and in the photographs provided to the Examiner with a Declaration under 37 C.F.R. §1.132 signed by Dr. Timothy Neuberger, and forwarded with the response to the Office Action dated November 5, 2004.

As noted above, the Examiner alleges that it would take undue experimentation for one skilled in the art to practice the invention, given the original scope of the claims. Applicants respectfully traverse the Examiner's assertion and have amended the claims as noted above to better clarify the invention. Based on these amendments, and on the support provided in the instant specification for enablement of these aspects of the invention, Applicants assert that it would not take undue experimentation for a skilled practitioner to practice the invention as currently claimed.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, is respectfully requested.

Rejections Under 35 USC § 112, second paragraph

Claims 19-27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 19 recites, "promoting growth or differentiation of neural precursor cells in vitro after injury to the neural cells". The Examiner notes that it is understood that "injury to the neural cells" occurs in an in vivo condition, not in vitro. Furthermore, the Examiner alleges that Applicant's recitation of "in vitro" along with "after injury to the neural cells" leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. In addition, the Examiner notes although the dependent claim 28 clarifies the subject matter of the independent claim 19 by "the neural precursor cells obtained from a mammal", it is considered that the meaning of the claims (claims 19-27) should be clear from the wording of the claim alone. As discussed above, the applicant's omission of essential step renders the claimed invention vague and unclear.

Applicants respectfully traverse the Examiner's rejection of claim 19, under 35 USC §112, second paragraph for being indefinite, whereby the Examiner objects to the use of the phrase "after injury to neuronal cells". However, Applicants have amended the claims to delete this phrase, solely for the purpose of moving this application along towards allowance.

Applicants assert that support for *in vitro* injury to neuronal cells can be found in the instant application on page 41, lines 26-30, continuing onto page 42, lines 1-12, which delineates the actual experimental protocol with glutamate. The immunostaining procedure using the antibodies specific for the neural precursor cell proteins, as currently claimed, is found on page 42, lines 13-30, continuing onto page 43, lines 1-13. As noted in the specification, the neural precursor cells obtained from the brains of embryonic rat pups were allowed to mature in culture for 10 days, at which time it is known to those skilled in the art that glutamate receptors are expressed on these mature neuronal cells. These cells are then injured by exposing the cells to glutamate, followed by incubation in the presence or absence of a compound of the present invention. After the specified time in culture, the cells were stained using antibodies specific for certain proteins (as currently claimed) that are characteristic of neural precursor cells as outlined in the specification.

However, as noted above, Applicants have amended claim 19 to recite:

"A method for promoting growth or differentiation of neural precursor cells in vitro, wherein said neural precursor cells express one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, the method comprising exposing said cells to an effective amount of a composition containing a compound having one of the following structural formulas....."

In light of the foregoing amendment, Applicants assert that the rejection under 35 USC §112, second paragraph is moot. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC § 102(b)

Claims 8-12, 19-23, 57, 67 and 69-72 are rejected under 35 USC §102(b) as being anticipated by Nair, *et al.* (US 4965284).

The Examiner's Position Regarding Nair et al.

The Examiner alleges that Nair teaches the use of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide for modulating the immune system; stimulating the proliferation and differentiation of blood cell progenitors in vitro or in vivo (bone marrow of warm-blooded animals); accelerating the recovery of white blood cell progenitors in vitro or in vivo (bone marrow of warm-blooded animals); and enhancing the activity of immune cells and/or immunoregulatory proteins, wherein said compound is administered to warm-blood animal or warm-blood animals conditioned to chemical or irradiation therapy in amounts ranging from about 5 mg to about 400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day (column 8, lines para. 1; column 12, lines 60-66; claims, especially claims 16-23).

Furthermore, the Examiner notes that although Nair is silent about the instantly required "promoting neural tissue regeneration or expression" (claim 8); "the tissue is of neuronal origin and the method is for promoting neural expression" (claim 10); "the administration is effective to promote the neural expression of one or more proteins selected from the group consisting of: eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4" (claim 12); "promoting recovery of behavioral function of neurons after a decrease in neural function" (claim 19); and "promoting regeneration of neural precursor cells" (claim 57), such properties or characteristic deem to be inherently presented in the referenced method. The Examiner alleges that where the administration of same compound (i.e., N-[4-[(4-

fluorophenyl) sulfonyl]phenyl]-acetamide) at overlapping dosage amounts (i.e. about 5 mg to about400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day) to same treatment population (i.e., "warm blooded animal", "warm blooded animal" conditioned to "chemical or irradiation therapy"), the instantly claimed mechanism of action must be inherently presented in the prior art (Nair). Therefore, the Examiner alleges that Nair anticipates the claimed invention.

Applicants' Invention as Currently Claimed

Applicants' invention is drawn to a method for increasing neural expression of one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4 on neural precursor cells ***in vitro***, comprising exposing said cells ***in vitro*** to an effective amount of a composition containing a compound having one of the structural formulas described in the present application.

In addition, Applicants' invention is also drawn to a method for promoting growth or differentiation of neural precursor cells ***in vitro***, wherein said neural precursor cells express one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, the method comprising exposing said cells ***in vitro*** to an effective amount of a composition containing a compound having one of the structural formulas described in the present application.

Furthermore, Applicants invention is drawn to a method for promoting growth and differentiation of neural precursor cells in a mammal in need of such therapy, or for increasing the number of neural precursor cells in a mammal at the site of injury, or for treating an injury to nervous system tissue, comprising

(a) administering a population of neural precursor cells obtained from a first mammal treated with a compound having one of the structural formulas as described in the present application;

b) collecting neural precursor cells expressing one or more proteins selected from the group consisting of eNCAM and nestin, from said first mammal and delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal in need of such therapy.

The neural precursor cells may be obtained from neural tissue, such as central nervous system tissue, or from the bone marrow. The neural precursor cells may also be

obtained from a normal mammal or from a mammal suffering from a contusion injury, a spinal cord injury, a surgical procedure, or an injury to nerve cells caused by an excitotoxic agent, such as glutamate.

Applicants' Position Regarding Nair et al.

Applicants respectfully traverse the Examiner's rejection under 35 U.S.C. §102(b) for the following reasons.

For example, as noted above for claims 8 and 19, the present application teaches methods for promoting growth or differentiation of neural precursor cells ***in vitro*** comprising exposing said cells ***in vitro*** to a composition containing a compound selected from a genus of compounds, wherein said contacting is effective to promote the growth or differentiation of neural precursor cells or to promote the expression of certain protein markers useful for tracking the genesis of neurons from neural stem cells or neural precursor/progenitor cells. These neural precursor cells are identified on the basis of expression of one or more proteins selected from the group consisting of : eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4.

Applicants assert that Nair et al. do not teach or suggest the *in vitro* administration of the compounds of the present invention, as currently claimed in amended claims 8 and 19, for the indications described in the present application. The studies by Nair et al. consistently teach and describe the administration of the compounds to a warm blooded animal for use as an immunomodulator or for accelerating recovery of hematopoietic blood cells after treating animals with chemotherapy or irradiation therapy. Nair et al. teach assays whereby **the animals are either untreated or are treated with the compounds of the invention, followed by removal of serum or removal of certain cell types from the animals to determine the *in vivo* effect of the compounds** on, for example, stimulation of a colony stimulating factor in the serum from the treated mice, or for monitoring ***in vivo* effects of the compounds on activation of macrophages,** such that certain cytokines are then released from these cells and assayed on other cell types in culture. Applicants respectfully assert that the Examiner has misconstrued the procedures utilized by Nair et al.

For example, the examiner's attention is directed to column 9, lines 34 through 60, whereby Nair et al. describe the assay for measuring the ability of the compounds to activate tumor inhibitory macrophages *in vivo*. As noted in column 9, lines 49-52, it states:

> "...% cytostasis=(A-B)/A X 100 were A=cpm of cultures containing normal control macrophages; and B=cpm of cultures containing experimental **macrophages obtained from compound-treated mice**."

Furthermore, IL-1 assays were conducted using peritoneal exudates cells from mice treated orally with the compounds. The Examiner's attention is drawn to column 9, lines 65-68 and column 10, lines 1-12, whereby it states:

> "**Groups of C57B1/6 mice were treated orally with immunomodulator** at doses of 25, 100 or 200 mg/Kg. Four days later peritoneal exudate cells (PEC) were collected and 1.times.10.sup.5 cells were plated in RPMI-1640 medium containing 5% fetal calf serum (FCS). After 2 hours incubation at 37.degree. C. the non-adherent cells were washed off and the adherent cells were incubated for 24 hours in RPMI medium with 5% FCS with or without Lipopolysaccharide (10 ug/ml). The following day the supernatants were collected and assayed for IL-1 on thymocytes. The cultures were incubated for 3 days and then pulsed with .sup.3 H-TdR using 0.5 .mu.Ci/well. The cells were harvested and the number of counts per minute (CPM) was determined using a Beckman scintillation counter."

In addition, **lymphocytes were obtained from normal mice or treated mice** and were tested for their ability to release an IL-2 like factor in culture. This is found in column 10, lines 61-68 continuing on to column 11, lines 1-2:

> "**Lymphocytes prepared from normal mice or mice treated with 100 mg/kg of test compound** were stimulated with Con A for 2 days. Culture supernatants were harvested and tested for putative IL-2 activity in 3 proliferation assays using thymocytes, lymphoblasts and CTLL-2 cells as indicators. Although supernatants from normal lymphocytes supported the growth of all indicator cells, lymphocytes from treated animals apparently produced more IL-2 as indicated by a greater degree of cell proliferation in all three test systems."

Furthermore, the anti sheep RBC assay was also performed by treating animals ***in vivo*** with vehicle or test compound, as shown in column 11, lines 19-30.

And finally, the effect of the test compounds on induction of a colony stimulating factor was also assessed **by obtaining serum from normal or treated animals**, as

shown in column 11, lines 62-68 and testing the serum from normal or treated mice on normal bone marrow cells in culture. This method differs substantially from the currently claimed *in vitro* methods.

Moreover, claim 8 has been amended to recite:

"A method for increasing neural expression of one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4 on neural precursor cells ***in vitro****, comprising exposing said cells* ***in vitro*** *to an effective amount of a composition containing a compound having one of the following structural formulas..."*

In addition, claim 19 has been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells ***in vitro****, wherein said neural precursor cells express one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, the method comprising exposing said cells* ***in vitro*** *to an effective amount of a composition containing a compound having one of the following structural formulas..."*

Based on the foregoing, Applicants assert that Nair et al. do not teach or suggest the methods of the present invention as currently claimed for ***in vitro*** use as shown above in amended claims 8 and 19, and any dependent claims based on these methods.

The instant application further teaches a method for promoting growth or differentiation of neural precursor cells comprising administering to a first mammal a neural growth or differentiation promoting effective amount of a composition, collecting neural precursor cells from the first mammal and delivering these cells to a site of injury in the first mammal or in a second mammal; wherein the composition comprises the compound from the genus described. Furthermore, the administering is effective to promote the expression of one or more proteins selected from the group consisting of : eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4.

Applicants assert that Nair et al do not teach or suggest the treatment of animals with the present compounds and removing the neural precursor cells that express the

protein markers for monitoring the genesis of neurons and then administering these neural precursor cells to a first or second mammal in need of such therapy, as presently claimed.

In addition, claim 57 has been amended as follows:

"A method for promoting growth and differentiation of neural precursor cells in a mammal in need of such therapy, comprising

(a) administering a population of neural precursor cells obtained from a first mammal treated with a compound having one of the following structural formulas.....

b) collecting neural precursor cells expressing one or more proteins selected from the group consisting of eNCAM and nestin, from said first mammal and delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal in need of such therapy."

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. 102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Nair et al. do not teach the *in vitro* methods of the present invention as currently claimed or the methods for neural precursor cell transplant from a donor animal to a recipient, as currently claimed. Applicants assert that there are distinct differences between the teachings of Nair et al. and the presently claimed invention.

For example, Nair et al. do not teach or suggest the use of this genus of compounds for growth or differentiation of neural precursor cells *in vitro*. Furthermore, Nair et al. do not teach or suggest that this genus of compounds could be used to treat neural precursor cells obtained from neural tissue or non-neural tissue to result in growth or differentiation of a population of neural precursor cells *in vitro,* which express proteins characteristic of neuronal precursor cells. Moreover, Nair et al. do not teach or suggest the use of this genus of compounds for treating injury to neural precursor cells *in vitro*. Nair et al. provide no teaching as to how one can obtain neural tissue for treatment with the compounds of this genus. Nor do Nair et al. teach or suggest how one can utilize the neural stem cells or precursor cells obtained from the bone marrow or from neural tissue to treat a mammal that has experienced an injury to nervous system tissue, for example, a contusion to the spinal cord.

Accordingly, Applicants assert that Nair et al. do not anticipate the present invention as currently claimed. Nair et al. do not teach or suggest the methods of the current invention for treating injury to neural cells by stimulating growth and differentiation of neural stem cells or precursor cells, nor do Nair et al. provide enablement as to how one may utilize these compounds for treating injury to neuronal cells or tissue. Nair et al. only teach the use of this genus of compounds for treating disorders in which the hematopoietic stem cell system is compromised, such as in cancer patients whereby the chemotherapy or irradiation therapy destroys hematopoietic stem cells, thus leading to a decrease in peripheral blood cell counts, resulting in neutropenia and susceptibility to infections following such therapies.

Applicants further assert that the rejection under 35 U.S.C. § 102(b) is improper in that the Nair et al reference is a non-enabling reference. As stated in In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

For example, Applicants assert that Nair et al. do not teach or suggest the use of the compound of the present invention for promoting the growth or differentiation of neural precursor cells *in vitro*, as currently claimed. As noted by the Examiner, Nair et al. specifically teaches the use of the claimed compounds for "modulating the immune system; stimulating the proliferation and differentiation of blood cell progenitors in bone marrow of warm-blooded animals". Furthermore, as also noted by the Examiner, Nair et al teach that the compounds are administered to warm-blood animal or warm-blood animals conditioned to chemical or irradiation therapy in amounts ranging from about 5 mg to about 400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day (column 8, lines para. 1; column 12, lines 60-66; claims, especially claims 16-23). Applicants assert that Nair et al. are silent as to the use of the compounds of the present invention for promoting the growth or differentiation of neural precursor cells *in vitro*.

In addition, Nair et al. do not teach or suggest the use of the compounds of the present invention for the transplant of neural precursor cells having the designated protein markers that establish that the cells are of early neuronal origin from a treated animal to a recipient (untreated) animal in need of such therapy, such as in an animal suffering from an injury to nervous tissue, such as, but not limited to, a spinal cord injury. Applicants further assert that the potential use of this class of compounds for stimulating the growth and differentiation of neural stem cells or precursor cells either *in vitro* or *in vivo* was not contemplated until the time of the present invention.

In light of the foregoing claim amendments and arguments, Applicants respectfully request withdrawal of the rejection. It is to be understood that the claims have been amended solely to place the application in condition for allowance. Applicants reserve the right to pursue the remaining subject matter in further Divisional applications.

Fees

A check in the amount of $60.00 is enclosed to cover the Petition for a one month extension of time. No other fees are believed to be necessitated by the present response. However, should this be in error, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

Veronica Mallon, Ph.D.
Agent for Applicants
Reg. No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07601
Tel: (201) 487-5800